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Elevated Transferrin Saturation, Health-Related Quality of Life and Telomere Length

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Abstract

We sought to examine the relationship between elevated transferrin saturation (TS) and measures of health status (telomere length and patient-reported health-related quality of life) to assess whether elevated TS is associated with negative patient outcomes beyond increased risk for morbidity and mortality, using a cross-sectional analysis of the Hemochromatosis and Iron Overload Screening Study supplemented with assays for leukocyte telomere length in adults ≥25 years old (n=669). Among individuals with elevated TS (≥45% for women and ≥50% for men), who also had a usual source of care, only 5.2% reported ever being told by a doctor that they had an elevated iron condition. In a fully adjusted general linear regression model controlling for demographic characteristics as well as health conditions associated with iron overload, elevated TS versus non-elevated TS was associated with worse general health status (60.4 vs. 63.8,

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As a cooperative agreement with the CDC, CDC personnel were involved in decisions regarding the design and conduct of the study as well as authorship of the manuscript.
Dr. Mainous had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Drs. Mainous, C. McLaren, G. McLaren, Diaz, Mr. Wright and Ms. Hulihan performed research. Drs. Mainous, C. McLaren, G. McLaren and Diaz designed the research study. Drs. Argraves and Twal provided the laboratory resources for running telomere assays and conducted the telomere assays. Drs. Mainous, C. McLaren, G. McLaren, Diaz, Grant, Ms. Hulihan and Mr. Wright analyzed the data. Dr. Mainous, Ms. Hulihan and Mr. Wright wrote the first draft of the paper and all coauthors significantly contributed to the completion of the final draft of the paper.

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p<0.05), mental health status (76.5 vs. 82.2, p<0.0001) and shorter telomere length (241.4 vs. 261.3, p<0.05). Increased surveillance of elevated TS may be in order as elevated TS is associated with decreased health status and very few patients with elevated TS are aware of their condition.

Keywords

Iron; telomere length; quality of life; functional status; health status

INTRODUCTION

Elevated percent transferrin saturation (TS) has been shown to be associated with downstream morbidity and mortality (Mainous et al, 2004, Wells et al, 2004, Mainous et al, 2005A, Mainous et al, 2005B, Mainous et al, 2013). Elevated iron stores, as represented by percent transferrin saturation (TS), can damage cells and tissues through oxidative stress, thereby contributing to disease incidence and severity (McCord, 1998, Sullivan, 2005). Increased risk of heart disease, diabetes, dementia, cancer, and death has been found among individuals with elevated TS (Mainous et al, 2004, Wells et al, 2004, Mainous et al, 2005A, Mainous et al, 2005B, Ellervik et al, 2011A, Ellervik et al 2011B, Ellervik et al, 2012, Mainous et al, 2013A, Wlazlo et al, 2013).

General measures of current health status have significant value by being useful outcome measures across a broad range of disease entities (Rumsfeld et al, 1999, Curtis et al, 2002). Telomere length is a general measure of health status attributed to its representation of biological aging, disease risk, and cumulative oxidative stress damage (Von Zglinicki, 2000, Mainous et al, 2010, Shammas, 2011, Codd et al, 2013, Cohen et al, 2013, Mainous et al, 2013B). Similarly, general self-assessed health-related quality of life measures are important health status outcomes for patients across diseases (Ware Sherbourne, 1992). The purpose of this study was to examine the relationship between elevated transferrin saturation, telomere length, and patient-reported health-related quality of life.

MATERIALS AND METHODS

We examined participants in the Hemochromatosis and Iron Overload Screening (HEIRS) Study, a multicenter, multiracial-ethnic sample of 101,951 primary care adults 25 years of age or older in the United States and Canada (HEIRS Protocol, 2001, McLaren et al, 2003, Gordeuk et al, 2008). Details of study design and sampling methods have been published and can be found in the HEIRS Protocol (HEIRS Protocol, 2001, McLaren et al, 2003, Gordeuk et al, 2008). Interview data were obtained from initial screening of all participants (n=101,951) and blood specimen data from a subsequent Comprehensive Clinical Exam (CCE) (n=2746) for subjects from the initial screening identified as having the genotypic or phenotypic indication of hemochromatosis or iron overload. DNA specimens were collected from each participant during the CCE and stored at the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) at the National Heart Lung and Blood Institute. For the current study we requested 1,157 of these DNA specimens from CCE subjects for telomere length assays as part of a larger study assessing relationships between elevated iron phenotype, genotypic hemochromatosis, and outcomes (Mainous et

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al, 2013B). The telomere data (n=1,146) were then merged with variables from the CCE that were contained in the HEIRS data sets.

Subjects

The final sample was comprised of individuals from the CCE with TS values, self-assessed health status measures, and known telomere length (n=669). Individuals who indicated that they were on a phlebotomy regimen prior to the CCE were eliminated because TS may reflect the impact of the phlebotomy and not represent a consistent TS level. Individuals missing TS, self-assessed health status measures or known telomere length were excluded, which lowered the sample size from 1,146 to 669.

Elevated Transferrin Saturation

We conducted analyses using three classification categories for transferrin saturation. The first two categories were gender-specific: men were considered to have elevated TS if their level was 50% or above while females were considered to have elevated TS if their level was 45% or higher, as described in the HEIRS Protocol, while subjects below these gender-thresholds were considered to have non-elevated TS (HEIRS Protocol, 2001, Gordeuk et al, 2008). The third category (TS ≥60% in either gender) was analyzed to assess a potential relationship between higher levels of TS and health status based on previous research showing worse morbidity and mortality outcomes with higher TS (Mainous et al, 2004, Wells et al, 2004, Mainous et al, 2005A, Mainous et al, 2005A, Ellervik et al, 2011A, Ellervik et al 2011B, Ellervik et al, 2012, Mainous et al, 2013A, Wlazlo et al, 2013).

Health Status Measures

Self-Assessed Health-Related Quality of Life—Subscales of the SF-36 Health Survey were used to measure general health (GH) and psychological well-being or general mental health (MH) in the HEIRS study (Ware Sherbourne, 1992). Subscale scores were calculated using standard scoring methods and the higher the score, the better the patient's reported health. The GH subscale has 5 items and asks subjects to rate their general health, how their health compares to others, and their future expectations of their health on 5 point scales. The MH subscale has 5 items and asks subjects to report how often they have been a very nervous person, felt down in the dumps, felt calm and peaceful, felt downhearted and blue, and been a happy person on 5 point scales. The sum of responses to each question is tabulated as a raw score, which is then standardized on a 100 point scale (Ware Sherbourne, 1992).

Telomere Length via real time PCR analysis—Leukocyte telomere length was measured with a quantitative PCR-based technique (qPCR) that compares telomere repeat sequence copy number to single-copy gene (36b4) copy number in a given sample (Cawthon, 2002, Zhao Fernald, 2005). Triplicate DNA samples were amplified in parallel in 20 μL reaction using SsoFast EvaGreen real-time PCR supermix (Bio-Rad, Hercules, USA) containing 20 ng of sample DNA. The telomere-specific reaction included 500 nM of telomere-specific primers (forward: 5'GGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGTT3'; reverse: 5'GGCTTGCCTTACCCTTACCCTTACCCTTACCCTTACCCT3'). The 36b4 reaction

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included 300 nM of the forward (5'CAGCAAGTGGGAAGGTGTAATCC3') and reverse (5'CCCATTCTATCATCAACGGGTACAA3') primers. The qPCR/primer supermix (19 ul) was aliquoted into PCR multiwell plates using an EpMotion 5070 robotic liquid handling unit (Eppendorf, Germany), and then 1 ul of sample DNA (20 ng) was added to each well. All qPCR reactions were run using a CFX96 real-time thermal cycler (Bio-Rad). The thermal cycling profile for both amplicons began with 95°C incubation for 3 min and then 30 cycles of 10 s at 95°C and 1 min at 58°C. The specificity of all amplifications was determined by melting curve analysis. A total of 14 study samples and 2 calibrator samples (all in triplicate) were processed per plate.

Analysis of qPCR data—Analysis of sample telomere length and 36b4 expression levels was done using the PCR Miner algorithm developed by Zhao and Fernald (Zhao Fernald, 2005). Values derived for telomere (T) were normalized for each sample with the corresponding expression of 36b4 gene (S) as T/S ratio.

Demographics

For the analyses, age was analyzed as a continuous variable (Fitzpatrick et al, 2011). We also evaluated gender and race-ethnicity as both are associated with telomere length (Adaikalakoteswari et al, 2005, Demissie et al, 2006, Nordfjäll et al, 2008, Xu et al, 2008, Fitzpatrick et al, 2011). As socio-economic status has been observed to be associated with quality of life and disease state, we controlled for primary socio-economic factors, including: subjects' health insurance status, educational attainment and patient-reported usual source of care (Miravitlles et al, 2011, Barnett et al, 2012).

Health Conditions

During the initial screening, patients reported whether a doctor had ever told them they had "Too much iron in your body, iron overload, or hemochromatosis." A variety of downstream health conditions related to elevated iron were also assessed in the HEIRS study and included previous diagnosis of liver cancer, cirrhosis, heart failure or coronary heart disease, arthritis, diabetes, and impotence/fertility problems.

Statistical analysis

Analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC). Comparisons of demographic characteristics between TS elevation categories were performed using chi-square (race-ethnicity, gender, education, usual source of medical care and insurance) and t-test (age). We examined the distributions of the three outcome variables (telomere length, MH, GH) by looking at the mean, median, skewness, kurtosis and Kolmogorov-Smirnov test and concluded that they differed slightly from a completely normal distribution. Consequently, we examined the relationship between TS and the three outcome variables using a Mann-Whitney U nonparametric test which was suited for non-normal distributions. Unadjusted values of the general health status subscale, mental health status subscale and telomere length were compared between TS elevation categories of elevated (≥50% for men; ≥45% for women) versus non-elevated (<50% for men; <45% for women) using a Mann-Whitney U nonparametric test. In an effort to see an impact of higher levels of TS we also compared individuals with TS ≥60% with the non-elevated group (<50% for men; <45% for

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women). Following the bivariate analyses, we also performed analyses in general linear regression models controlling for the demographic characteristics of age, gender, race-ethnicity, usual source of medical care, education, and health insurance. In multivariate analyses to control for potential confounding variables we used a general linear regression model which is robust for distributions that vary slightly from normality. A final set of general linear regression models controlled for demographic characteristics as well as the patient-reported and/or biopsy-diagnosed health conditions of liver cancer, cirrhosis, heart failure or disease, arthritis, diabetes, patient-reported elevated iron or iron overload and impotence/fertility problems.

RESULTS

Demographic characteristics of the sample are featured in Table 1. Among all subjects in the sample (n=669), mean general health was 61.7 (range: 0–100, SD +/− 22.8), mean mental health was 79.1 (range: 8–100, SD +/− 18.0), and mean telomere length 250.8 (range: 58–967, SD: 97.1). Among individuals with elevated TS (≥45% for women and ≥50% for men), only 4.97% reported that they had “Too much iron in your body, iron overload, or hemochromatosis.” Even among individuals with elevated TS who have a usual source of care, only 5.23% had knowledge of having elevated iron suggesting that the vast majority of individuals with elevated TS are not being identified.

Table 2 shows that elevated TS is associated with worse general health status, mental health status and shorter telomere length in crude analyses, analyses adjusting for demographics and a full model adjusting for demographics and health conditions.

When TS is elevated ≥60% and is compared to individuals with non-elevated TS (<50% for men; <45% for women), in unadjusted analyses general health status is worse (55.1 vs 64.3, p<.001), mental health status is worse (75.3 vs 81.7, p<.01), and telomere length is shorter (238.1 vs 263.7, p<.01). In a fully adjusted model controlling for demographics, socio-economic, and disease covariates, individuals with TS elevated at ≥60% still had worse general health status (58.1 vs 63.8, p<.01) and worse mental health status (75.6 vs 82.2, p<.01), compared to individuals with non-elevated TS. The fully adjusted mean difference in GH between the ≥60% TS individuals and the non-elevated individuals was 5.7 while the mean difference between the ≥45/50% TS individuals and the non-elevated individuals was 3.4, indicating a greater impact of TS on GH with higher levels of TS. Similarly, the fully adjusted mean difference in MH between the ≥60% TS individuals and the non-elevated individuals was 6.6 while the mean difference between the ≥45/50% TS individuals and the non-elevated individuals was 5.7, indicating a greater impact of TS on MH with higher levels of TS. Telomere length was no longer statistically significantly different between the ≥60% TS group and the non-elevated group in the fully adjusted model (243.8 vs 261.3, p=.21).

DISCUSSION

The results of this study show that elevated TS levels are associated with a variety of current health status markers that are not limited to specific diseases. These associations exist even

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after controlling for demographic confounding variables like health insurance, age and race-ethnicity as well as common health conditions associated with hemochromatosis and iron overload. This study extends our knowledge of the associations between elevated TS and health status.

TS is an easily assessed, but not commonly ordered, biomarker for disease risk. Very few individuals (5%) of those in this sample who had elevated TS had any recognition that they had been told by a physician that they had elevated iron. Unfortunately, even among those with a usual source of care the proportion aware of their condition remained at 5%. The present results show that elevated TS is associated with a corresponding deficit in health-related quality of life in a general sense. Consequently, there may not be a specific sign or symptom (e.g., abdominal pain), related to elevated iron, that would make the physician suspect elevated iron as the potential cause for the patient's decreased health status. When the results of this current study are interpreted in the context of recent evidence indicating that patients with elevated TS are likely to have longer lengths of stay in the hospital, they suggest that elevated TS may be an under-recognized predictor of a patient's health status (Mainous et al, 2013A). Greater surveillance of the presence of elevated TS may be useful, especially among patients with low health-related quality of life, in notifying patients of their iron status and driving patient behavioral change to reduce iron load (Heath et al, 2008, Bao et al, 2012).

This study had several limitations that impact the generalizability of the results. First, this study was cross-sectional and thus allowed the researchers to evaluate associations only. Second, although a significant, independent association between elevated TS and worse health status was found even after controlling for demographics and a variety of health conditions associated with elevated iron, there may have been some residual confounding from unmeasured variables.

In conclusion, this study suggests that elevated TS is associated with worse patient-reported health-related quality of life with respect to both physical and mental indicators, as well as shorter telomere length. Recent data indicate that shorter telomere length has a causal role in development of diseases thus increasing the value of the finding that elevated TS was associated with shorter telomere length (Codd et al, 2013, Cohen et al, 2013). These findings add to the growing body of literature suggesting that increased attention to elevated TS in the health care environment in adults with nonspecific decreases in functional status may be in order.

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Abbreviations

TS	Transferrin saturation
HEIRS	The Hemochromatosis and Iron Overload Screening Study
SF-36	The MOS 36-item short-form health survey
GH	General health status
MH	Mental health status

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Table 1

Demographic and Socio-economic Covariates by Transferrin Saturation (TS) Percentage

Covariate	TS ≥45% for women and ≥50% for men	TS <45% for women and <50% for men	p
Sample size n=669	50.2	49.8	
Age (mean years)	56.8	55.6	=0.29
Race-ethnicity (%)			<0.001
Non-Hispanic White	42.3	63.1	
Non-White	57.7	36.9	
Gender (%)			<0.01
Female	43.2	53.2	
Educational Attainment (%)			0.36
<High School	14.3	10.8	
High School	24.7	23.8	
Some college	31.7	34.9	
Bachelors deg.	14.0	11.5	
Post-graduate	15.3	19.0	
Usual source of medical care (%)			0.96
Yes	94.9	94.8	
Health insurance (%)			
Insured	77.6	83.8	<0.05

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Table 2

Comparison of Mean General Health Scores, Mental Health Scores and Telomere Length by Transferrin Saturation (TS) Percentage

% TS	General health		Mental health		Telomere length	
Unadjusted	Mean	P	Mean	P	Mean	P
<45 for women and <50 for men	64.3		81.7		263.7	
≥45 for women and ≥50 for men	59.2	<0.01	76.6	<0.001	238.0	<0.001
Adjusted*	Mean	P	Mean	P	Mean	P
<45 for women and <50 for men	64.3		82.1		262.7	
≥45 for women and ≥50 for men	60.0	<0.05	76.7	<0.001	240.2	<0.01
Adjusted†	Mean	P	Mean	P	Mean	P
<45 for women and <50 for men	63.8		82.2		261.3	
≥45 for women and ≥50 for men	60.4	<0.05	76.5	<0.0001	241.4	<0.05

*Adjusted for demographics (age, gender, race-ethnicity, education, health insurance, and usual source of medical care).

†Adjusted for demographics and diseases (liver disease, diabetes, heart disease or failure, impotence/fertility problems, arthritis, and reported iron overload condition).